KCL Division of Women's Health

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An Academic Health Sciences Centre for London

Pioneering better health for all

Tommy's

Molecular mechanisms of renal dysfunction and hypertension secondary to neonatal hyperleptinaemia

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Guy's and St Thomas' NHS Foundation Trust

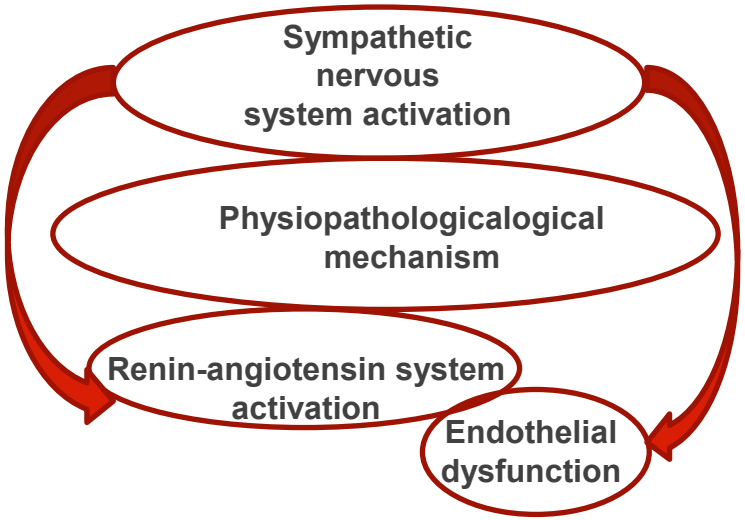
King's College Hospital NHS Foundation Trust

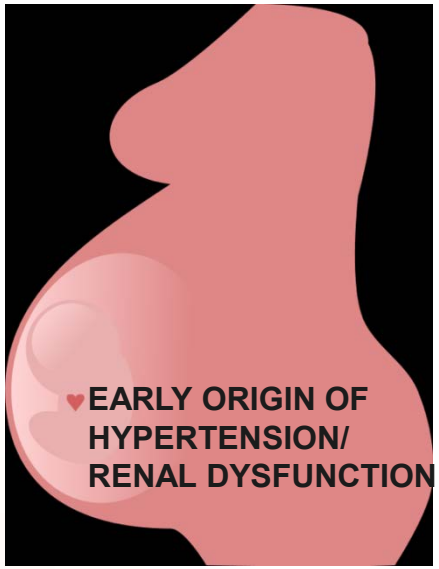
South London and Maudsley NHS Foundation Trust

Maternal obesity imprint cardiovascular, renal and metabolic dysfunction in the offspring

Maternal Causes

- Hyperinsulinaemia
- Adipokine dysregulation (leptin↑)
- Psychological stress
- Oxidative stress
- Inflammation





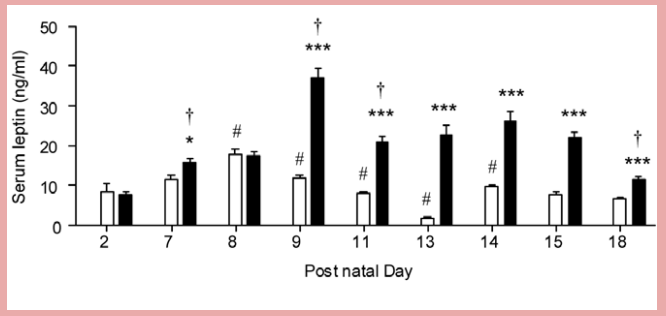
Fetal Causes

- Baroreflex impairment
- Renal afferent nerve activation
- Nephrogenesis
- Nephron hyperfiltration
- Inflammation
- Oxidative stress

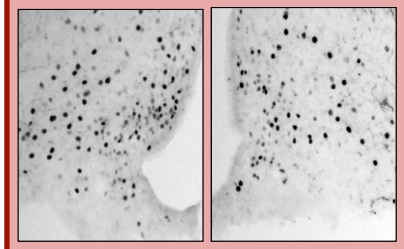
Maternal Obesity and Neonatal Leptin

Origin of SNA mediated hypertension

A. Neonatal leptin surge



B. ARC pSTAT3



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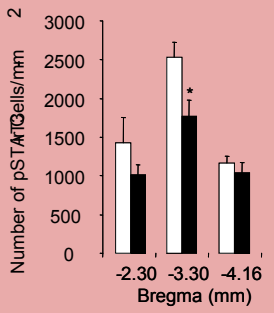


NEONATAL LEPTIN

Early Onset Hypertension
Sympathetic Overactivity
Hyperphagia
Cardiac Dysfunction
Renal Function?

Kirk et al 2009, PlosOne, Samuelsson et al 2013, Hypertension

Renal dysfunction in animal models

Maternal UN/GDM- Reduced nephron number, increased Na reabsorption, activation of RAS and oxidative stress

Maternal HF diet -Salt-induced hypertension, Na-ATPase activity, no serological evidence

Renal proximal tubule Na+ reabsorption ➡ extracellular volume ➡ BP

-Na-ATPase

-Na^+/H^+exchanger isoform 3 (NHE3)-PT

-Na^+-K^+-Cl- cotransporter (NKCC2a and b) –TAL

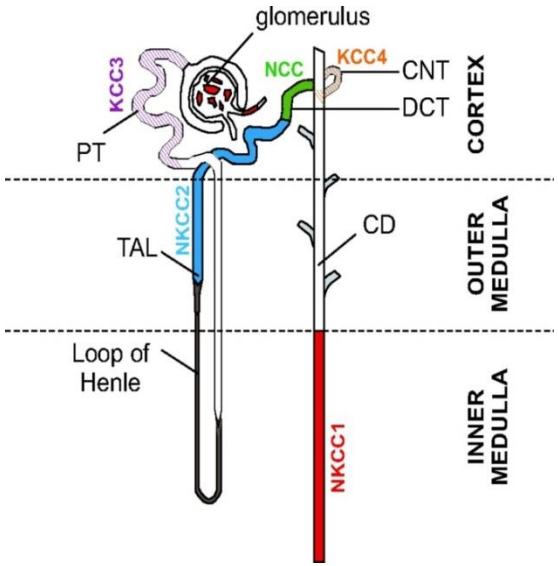
Regulation of sodium homeostasis

-Reactive oxygen species (ROS)

-Ang II

-Cyclo-oxygenase 2 (COX2)

-RSNA



High RSNA ➡ Kidney ischemia ➡ Intrarenal RAS ➡ Hyperfiltration ➡ Renal disease

(Merlet-Benichou C et al 1994)(Jones SE et al 2001)(Gilbert JS et al 2005)(Armitage 2005) (Rudyk et al 2000)

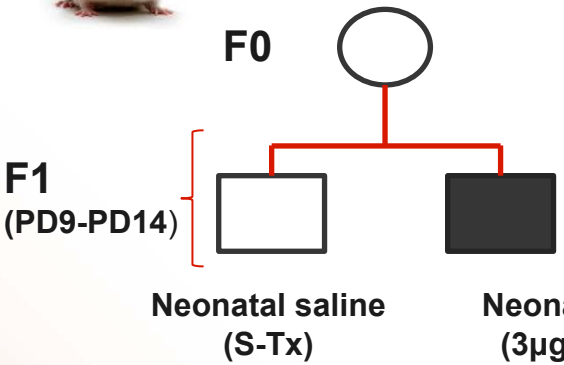
Aim

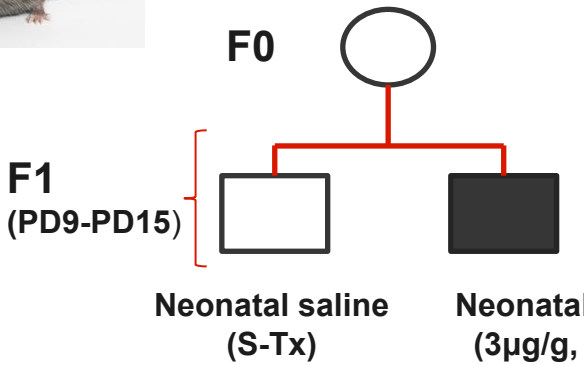
To investigate if exposure to elevated leptin in early postnatal life may permanently influence renal function due to altered renal sympathetic nerve activation, oxidative status, and renal vascular smooth muscle responses

Study Design

Sprague-Dawley rats

C57Bl/6 mice





F1
(1-2 month)

- Telemetry surgery
- Renal Denervation (RD and SH)
- *Renal Function before and after RD*
- Renal Myography

F1
(6 month)

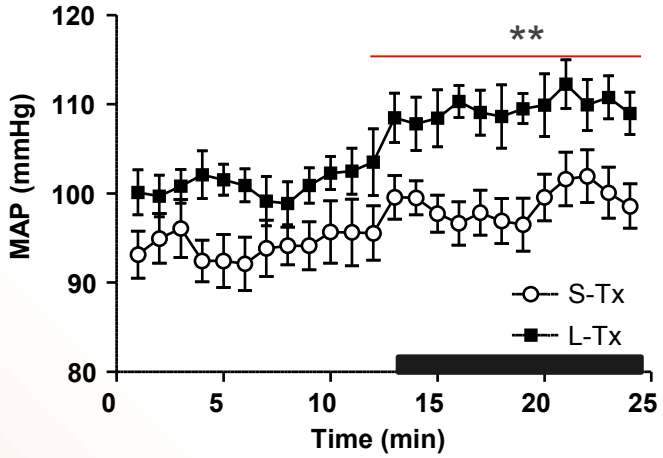
- Telemetry surgery
- Renal Function
- Renal QPCR

F1
(6 month)

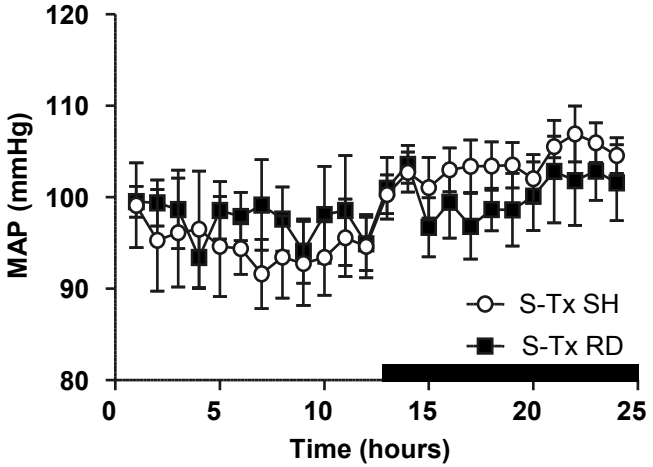
- Renal Function
- Salt loading

Hypertension-Unilateral Renal Denervation

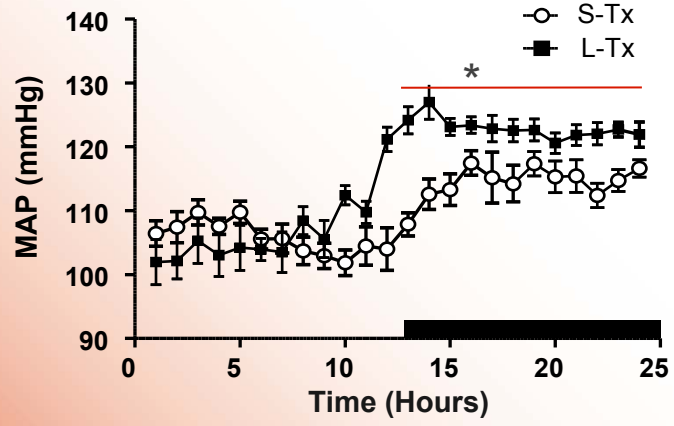
1 month old male rats

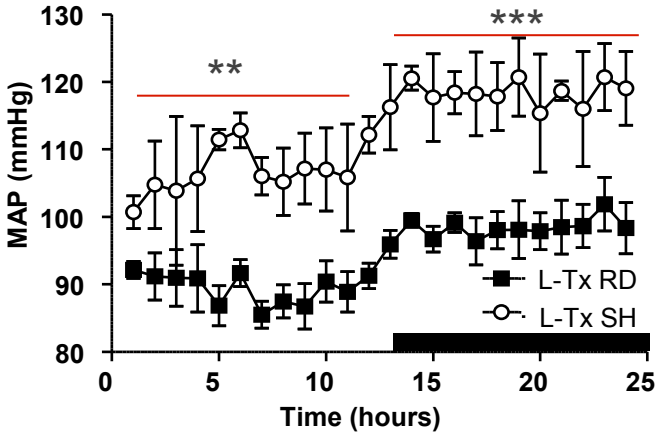


Renal Denervation



6 month old male mice

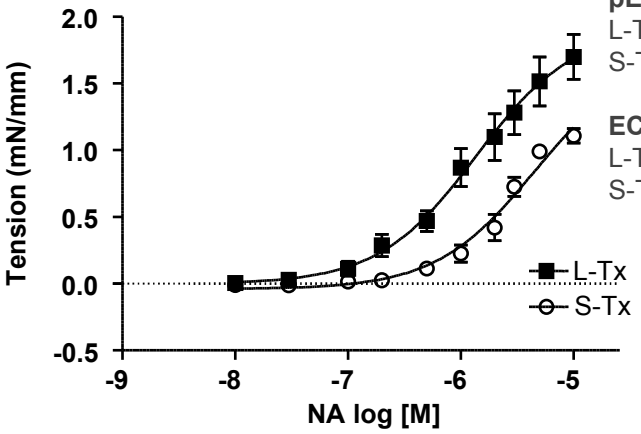




***P<0.001, **P<0.01, *P<0.05 (repeated ANOVA t test). Data are presented as mean ± SEM; n=4-8 per group.*

Renal Artery Myography in the early-hypertensive phase (1 month old)

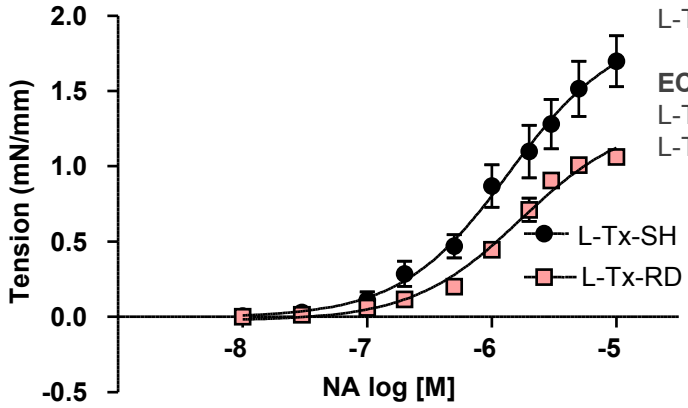
Noradrenaline



pEC_{50}
L-Tx, 5.8±0.1
S-Tx. 5.4±0.1,P<0.05

ECmax
L-Tx, 1.7±0.1
S-Tx,1.1±0.1, P<0.01

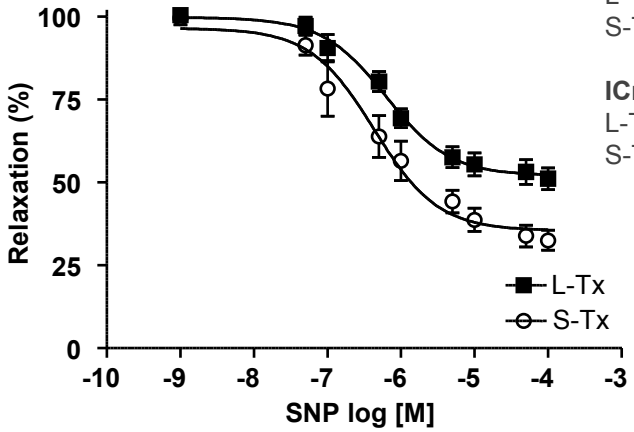
Renal Denervation



pEC_{50}
L-Tx-SH, 6.0±0.1
L-Tx-RD, 5.6±0.1, P<0.05

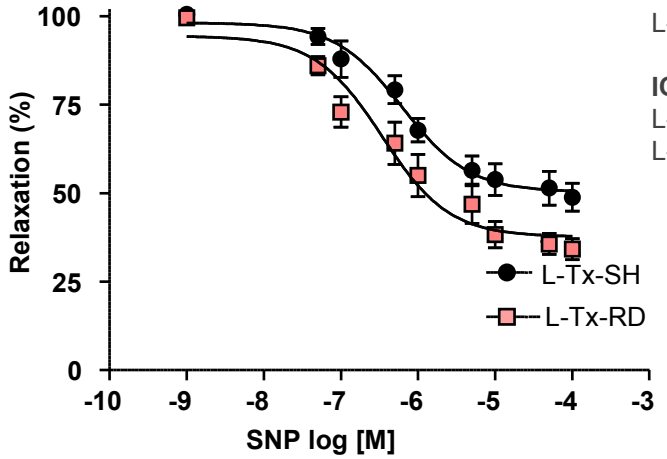
ECmax
L-Tx-SH, 1.8±0.1
L-Tx-RD, 1.2±0.1,P<0.05

Sodium nitropruisside



pIC_{50}
L-Tx, 6.2±0.1
S-Tx. 6.4±0.1,ns

ICmax
L-Tx, 49±9
S-Tx, 67±6, P<0.01

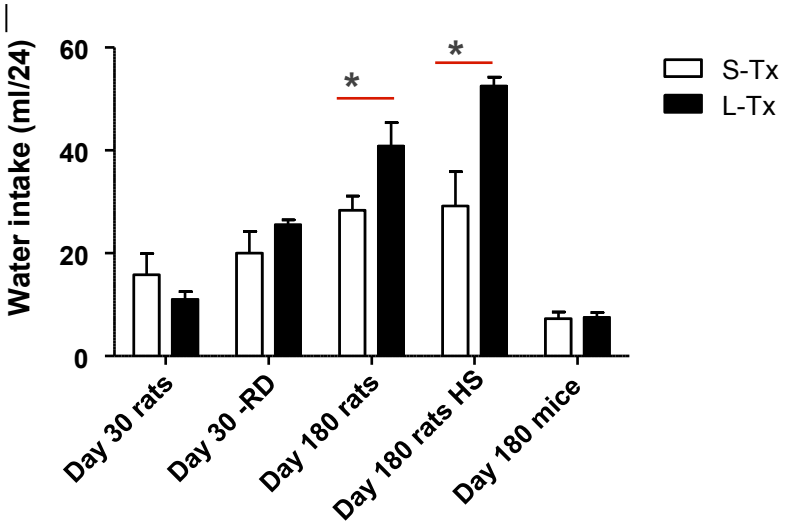


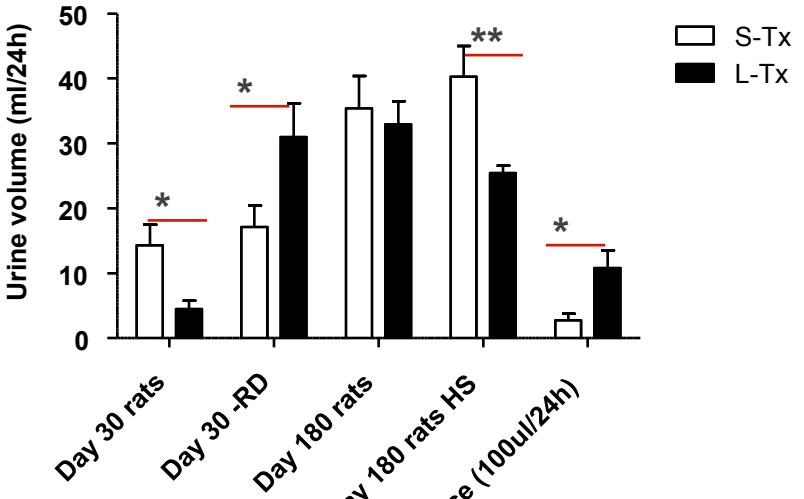
pIC_{50}
L-Tx-SH, 6.3±0.1
L-Tx-RD. 6.4±0.1,ns

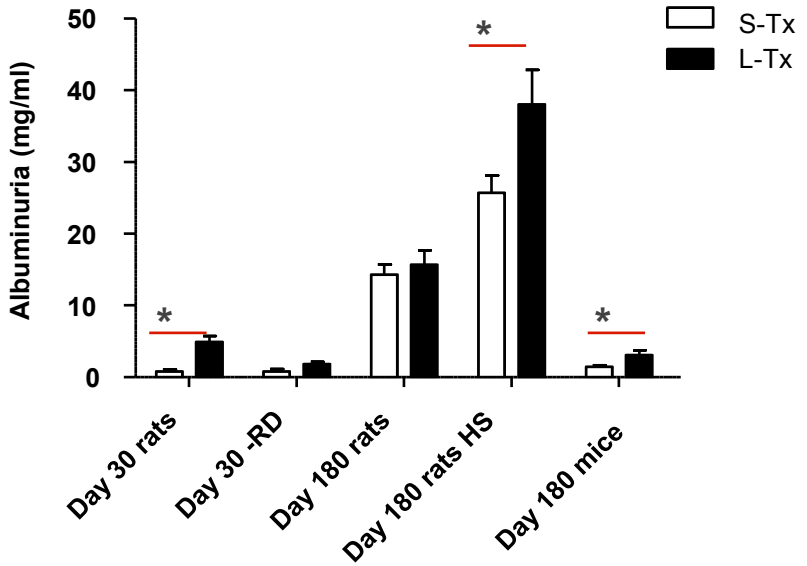
ICmax
L-Tx-SH, 48±3
L-Tx-RD, 62±2, P<0.05

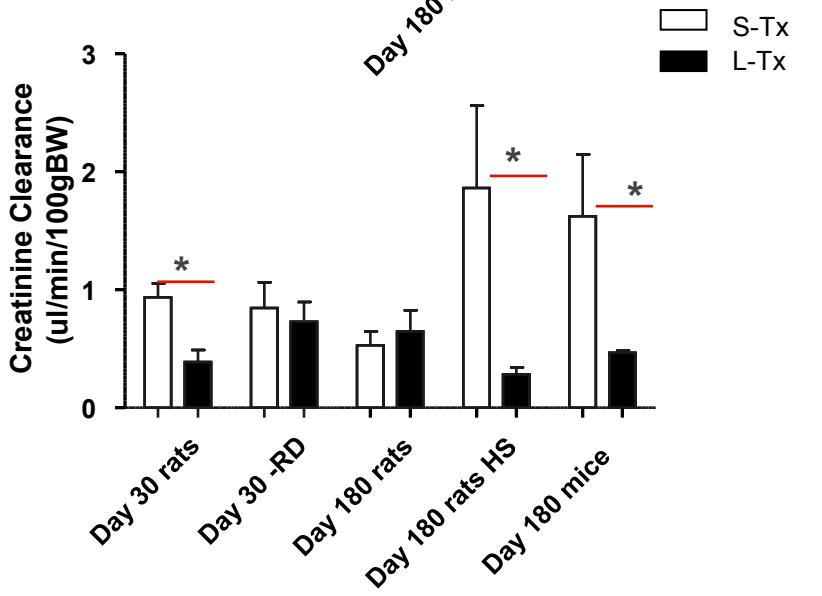
Data are presented as mean ± SEM; n=4-8 per group, t-test.

Renal Function and Salt Challenge



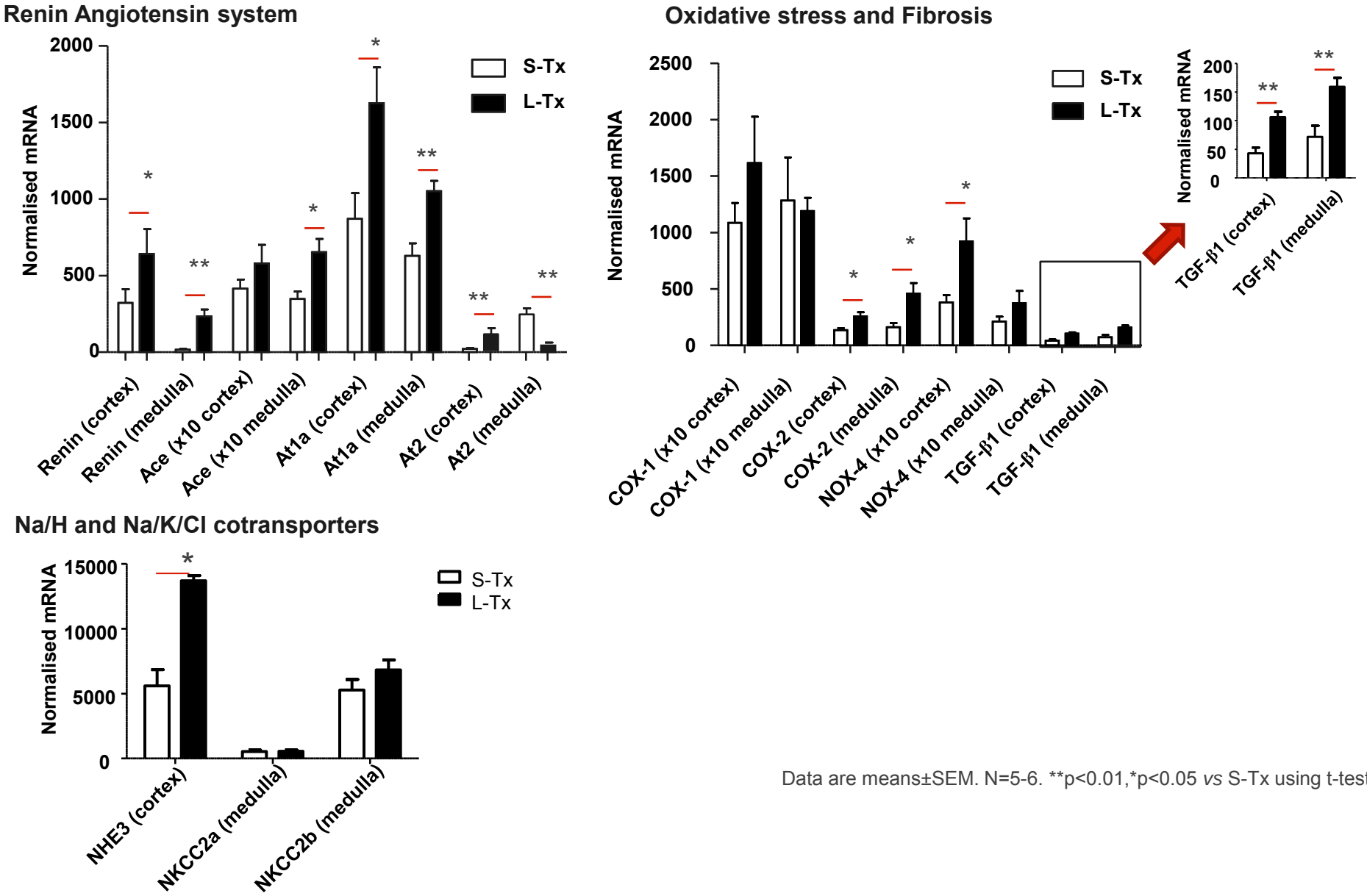






*Data are presented as mean ± SEM; n=4-8 per group,*P<0.05, t-test.*

Intrarenal expression of RAS, oxidative stress component and sodium transporters at established-hypertension phase



Data are means±SEM. N=5-6. **p<0.01,*p<0.05 *vs* S-Tx using t-test

CONCLUSION

Neonatal leptin treatment (L-TX) *led to*

- *Hypertension*
- ↑ MAP *before* obesity.
  - Enhanced contractile response in 2 nd order renal arteries
  - Renal nerve denervation of left kidney showed beneficial effects (normalised the blood pressure and artery function) illustrating the important role of renal sympathetic overactivity in this model
- *Renal parameters during early hypertensive phase (1 month) showed decreased creatinine clearance. L-Tx rats had significant albuminuria which was totally suppressed by renal denervation.*
- *The renal physiology during established hypertension phase (6 months) showed significant decrease in creatinine clearance, accompanied by an expanded plasma volume and urine albuminuria.*

CONCLUSION II

Neonatal leptin treatment (L-TX) *led to*

- *Altered renal RAS, sodium transport and oxidative stress markers during established-hypertension phase*

  - Increased renal RAS, Cox-2 and Nox-4 may affect renal microvasculature and Na^+ sodium reabsorption via Na^+ ATPase contributing further to the permanent hypertensive state.

Thanks to

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